

## SHORT COMMUNICATION

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## A clinical and molecular study of a patient with Simpson-Golabi-Behmel syndrome

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**Abstract** Simpson-Golabi-Behmel syndrome (SGBS) is one of the overgrowth syndromes. Microdeletions of the glypican-3 (*GPC3*) gene were described by Pilia et al. (1996). Glypican-3 encodes a putative extracellular proteoglycan which is expressed in embryonic mesodermal tissues and plays an important role in embryonal growth. We report a Japanese patient with SGBS who had a single base deletion in the exon 7 of the *GPC3* gene. This is the first report of a single base deletion of the *GPC3* gene.

**Key words** Simpson-Golabi-Behmel syndrome · Overgrowth syndrome · Glypican-3 · IGF-2 · Proteoglycan

### Introduction

Simpson-Golabi-Behmel syndrome (SGBS) is one of the overgrowth syndromes. Simpson et al. (1975) reported a new syndrome with the following features: broad stocky appearance, characteristic facies (large protruding jaw, broad nasal bridge, upturned nasal tip), macroglossia, and broad, short hands and fingers. Intelligence was normal. Golabi and Rosen (1984) and Behmel (1984) reported further patients. Garganta and Bodurtha (1992) published a review of the syndrome. Patients often attain a height of

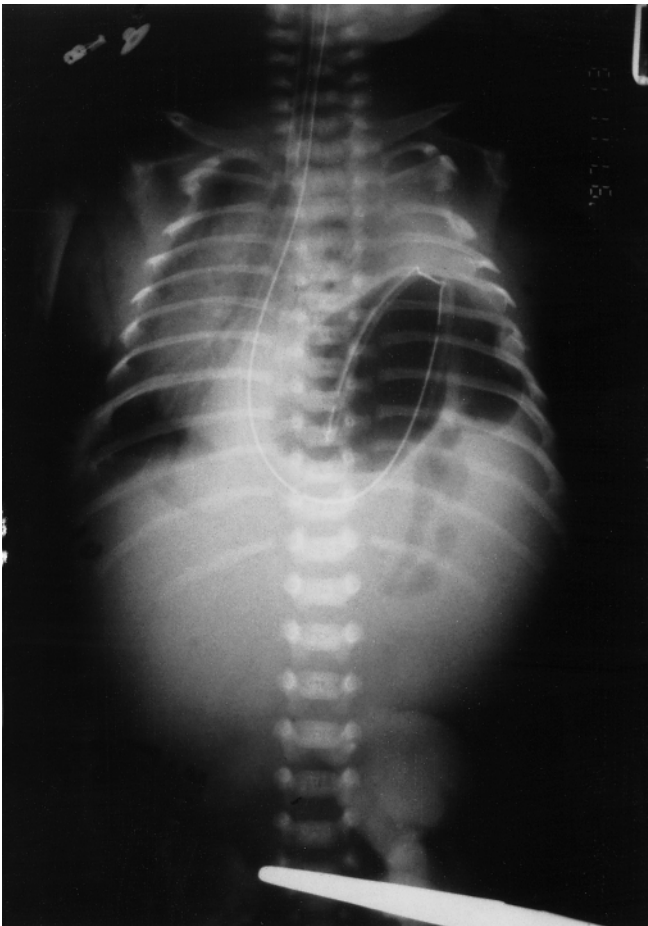
more than 195 cm. Xuan et al. (1994) mapped the gene of SGBS to Xq25-q27. Pilia et al. (1996) identified breakpoints in two female patients with X/autosomal translocations. The breakpoints occurred near the glypican-3 gene (*GPC3*; MIM300037), which spans more than 500 kb in Xq26. Glypican-3 encodes a putative extracellular proteoglycan which is expressed in embryonic mesodermal tissues and plays an important role during embryonal growth. It is linked to the cell membrane via glycosyl-phosphatidylinositol. It has putative glycosaminoglycan attachment sites and modulates insulin-like growth factor (IGF)-2 activities. Pilia et al. (1996) reported deletions encompassing exons of the *GPC3* gene, and Hughes-Benzie et al. (1996) added other deletions. However, Lindsay et al. (1997) reported that large-scale deletions in the *GPC3* gene may account for a minority of cases. We report a patient with SGBS who had a single base deletion in the *GPC3* gene.

### Case report

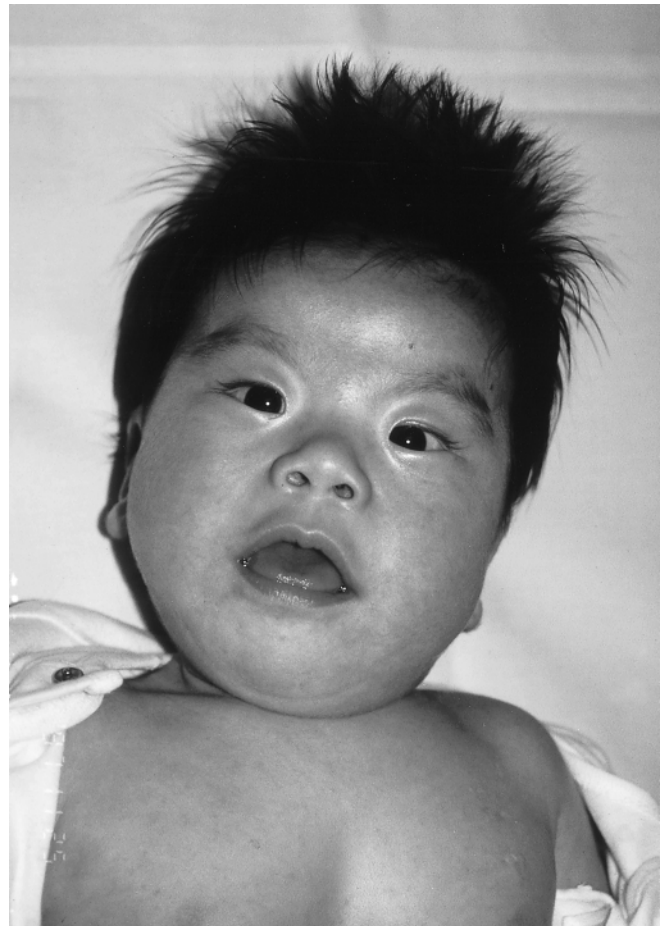
A male neonate was referred to the Pediatric Surgery Department because of congenital diaphragmatic hernia diagnosed by fetal ultrasonography. His birth weight was 3524 g at 36 weeks gestation (+2.4 SD). The left thoracic cavity was occupied by abdominal organs (Fig. 1). Respiratory care and surgical repair was carried out. SGBS was diagnosed because of somatic overgrowth and the characteristic facial appearance, including hypertelorism, macroglossia, central tongue groove, and high arched palate (Fig. 2). When the infant was 2 months of age, right diaphragmatic hernia was noted and a second operation was done. The bilateral occurrence of diaphragmatic hernia was a unique complication. He had funnel chest and inguinal hernia. At 21 months of age, he showed moderate overgrowth and mild developmental delay.

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**Fig. 1.** Roentgenogram showing congenital diaphragmatic hernia



**Fig. 2.** Facial appearance of the patient, with macroglossia and hypertelorism (Informed consent was obtained for the use of this photograph.)

## Materials and methods

DNA from peripheral leukocytes was obtained by standard methods. The exon/intron structures of *GPC3* and PCR primer pairs for mutation analysis have been reported by Huber et al. (1997). PCR amplification of each exon was performed, using the primers reported by Pilia et al. (1996) and Huber et al. (1997). Sequence analysis of the PCR products was done by the dye-terminator method (ABI auto-sequencer model 373A; Perkin-Elmer, Norwalk, CT, USA).

## Results

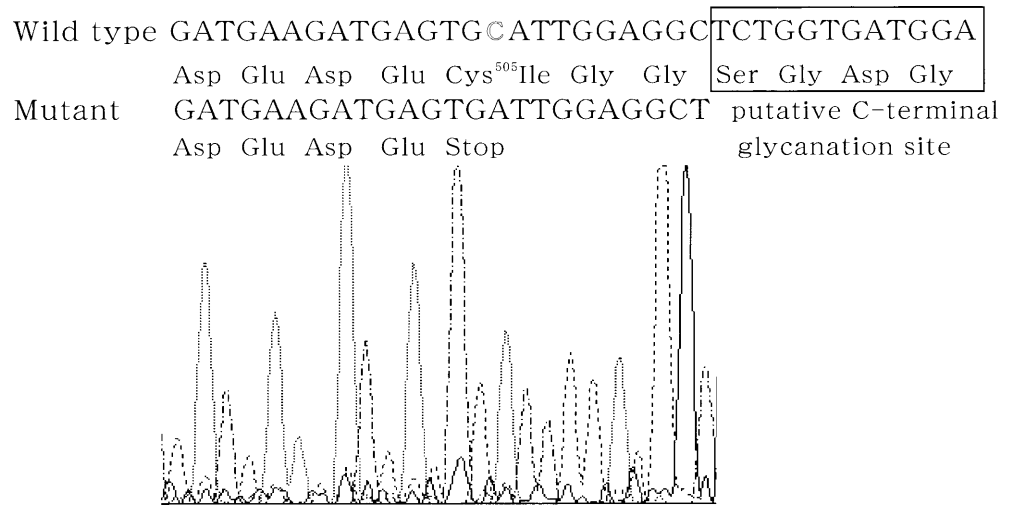
Large-scale deletion seemed to be less likely, as PCR amplification of each exon was successfully performed (data not shown). Direct sequencing of PCR products was done with the forward primers reported by Huber et al. (1997). One base deletion creating a premature stop codon in exon 7 was found (Fig. 3). Seventy-six C-terminal amino acids, including the putative glycanation site and glycosyl phosphatidylinositol transfer site, were lost. This truncated protein would not be anchored to the cell membrane.

## Discussion

There has been only one report on SGBS from Japan (Tsukahara et al. 1984). This syndrome is not extremely rare in Japan, as we have encountered three other unrelated patients at our institution during the past 5 years. Patients with SGBS may remain undiagnosed, or they may be misdiagnosed with other overgrowth syndromes, such as Beckwith-Wiedemann syndrome. Perlman syndrome, an autosomal recessive overgrowth syndrome with enlarged dysplastic kidneys, is another differential diagnosis (Verloes et al. 1995). We must consider SGBS in patients with characteristic facial appearance, multiple anomalies, and somatic overgrowth. Chest roentgenogram may be necessary if they have respiratory symptoms. However, diagnosis by this method is sometimes difficult, based on the dysmorphic aspects only. Molecular analysis of the *GPC3* gene may be a useful method for making an accurate diagnosis of SGBS.

Pilia et al. (1996) found *GPC3* gene deletions in three of six patients with SGBS, and Hughes-Benzie et al. (1996) reported four further deletions. The mutations in *GPC3* were unique deletions, ranging from less than 0.1 kb to more

**Fig. 3.** Sequence analysis of exon 7 of *GPC3*. Boxed area in the wild-type allele indicates the putative C-terminal glycanation site. One base deletion (1712delC) changed a cysteine residue to a premature stop codon (Cys505stop). The nucleotide number is in accordance with the report by Huber et al. (1997)



than 300kb in length, with no evidence of a mutational hot spot discerned (Pilia et al. 1996). However, Lindsay et al. (1997) found only five deletions in 18 SGBS patients and reported that large-scale deletions in the *GPC3* gene may account for a minority of cases. Recently, Xuan et al. (1999) reported a 13-base pair deletion in the *GPC3* gene in a Dutch-Canadian SGBS family. They showed that a discrete *GPC3* disabling mutation is sufficient to cause SGBS. Our result shows that a single base deletion in the *GPC3* gene may be responsible for SGBS, without large-scale deletions.

The mechanism of overgrowth in SGBS is still unknown. Pilia et al. (1996) showed that *GPC3* binds IGF-2 and modulates its activities. Overexpression of IGF-2 has been implicated in the pathogenesis of Beckwith-Wiedemann syndrome and in the newly established “IGF-2 overgrowth disorder” (Morison et al. 1996). However, Song et al. (1997) reported that *OCI-5*, the rat homologue of *GPC3*, interacts with fibroblast growth factor (FGF)-2, but not with IGF-2. The interaction was mediated by heparan sulfate chains of *OCI-5*. It is possible that *GPC3* interacts with other growth factors or proteins that regulate IGF-2 activity.

There is no apparent correlation between the extent of the deletions and the phenotypic expression (Neri et al. 1998). Deletions spanning exons or frame shift mutations are very likely to diminish the function of *GPC3* protein. As in our patient, protein lacking the putative C-terminal glycanation site and the glycosyl phosphatidylinositol transfer site is very likely to lose its stability and interaction. Accumulation of other types of mutations will give us further information on the function of *GPC3* and its clinical relevance.

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